

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of : BERNSTEIN, Joel E.
Serial No. : 10/813,760
Filed : March 31, 2004
For : COMPOSITIONS WITH REDUCED
HEPATOTOXICITY
Examiner : KWON, Brian Yong S.
Art Unit : 1614
Customer number : 23644
Confirmation No. : 5267
Attorney Docket No. : 41959-102739

APPEAL BRIEF

Commissioner of Patents and Trademarks
PO Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This appeal is from the Examiner's final Office Action mailed August 6, 2009, and the Advisory Action mailed October 5, 2009, in which pending claims (namely, claims 1-3, 5-9 and 11-15) were rejected. A timely Notice of Appeal was filed with the required fee October 7, 2009.

This brief is being filed along with the required \$270 fee pursuant to 37 C.F.R. §41.20(b)(2) that should be deducted from Deposit Account No. 12-0913.

(i) Real Party of Interest

The Real Party of Interest is Winston Laboratories, Inc. The Assignment is recorded at Reel 015164, Frame 0716.

(ii) Related Appeals and Interferences

Appellant is not aware of any related appeals or interferences.

(iii) Status of Claims

This is a U.S. non-provisional application. Thirty-seven claims were filed. Claims 4, 10 and 24 are cancelled. Claims 16-23 and 25-37 are withdrawn.

Claims 1-3, 5-9 and 11-15 are on appeal.

(iv) Status of Amendments

An Office Action with a final rejection was issued August 6, 2009. An amendment and response to the final Office Action was filed September 4, 2009. An Advisory Action was issued October 5, 2009, entering the amendment. A Notice of Appeal was filed October 7, 2009. The claims entered from the September 4, 2009 amendment are on appeal.

(v) Summary of Claimed Subject Matter

Claim 1

Claim 1 relates to a composition consisting essentially of one or more compounds at doses known to be hepatotoxic combined with about 5 mg to about 500 mg methionine along with about 10 mg to about 500 mg nicotinamide in a pharmaceutically acceptable carrier used in treatment of human disease. [0005, 0009]¹

Claim 2

Claim 2 is dependent on claim 1, relates oral ingestion. [0008]

¹ Citations are to numbers of paragraphs in the patent application as filed.

Claim 3

Claim 3 is dependent on claim 2, relates a composition of a solution, suspension, tablet, capsule and caplet. [0008]

Claim 5

Claim 5 is dependent on claim 3 and relates a composition of a sterile solution and a suspension. [0008]

Claim 6

Claim 6 is dependent on claim 1 and relates to suitability of the composition for intramuscular, intravenous or intrathecal injection. [0008]

Claim 7

Claim 7 is dependent on claim 1 and relates to folic acid amounts. [0007, 0009]

Claim 8

Claim 8 is dependent on claim 7 and relates to oral ingestion. [0008]

Claim 9

Claim 9 is dependent on claim 8 and relates a solution, suspension, tablet, capsule and caplet. [0008]

Claim 11

Claim 11 is dependent on claim 9 and relates a sterile solution and a suspension. [0008]

Claim 12

Claim 12 is dependent on claim 11 and relates intradermal, subcutaneous, intramuscular, intravenous and intrathecal injection. [0008]

Claim 13

Claim 13 relates to a composition consisting essentially of one or more standard doses of a hepatotoxic compound, wherein said hepatotoxic compound is selected from the group consisting of acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium, and valproic acid and wherein the hepatotoxic compound is combined with about 5 mg to about 500 mg methionine along with about 10 mg to about 500 mg nicotinamide in a pharmaceutically acceptable carrier used in treatment of human disease. [0006, 0007]

Claim 14

Claim 14 is dependent on claim 13 and relates to acetaminophen. [0009]

Claim 15

Claim 15 is dependent on claim 14 and relates to a dose of 80-1000 mg. [0009]

Claims 4, 10 and 24 are cancelled. Claims 16-23 and 25-37 are withdrawn.

(vi) Grounds of Rejection To Be Reviewed on Appeal

There is only one rejection at issue:

Claims 1-3, 5-9, and 11-15 were rejected under 35 U.S.C. 103(a) over Kroger et al., in view of Ogata et al., and Murdock.

(vii) Argument

A PRIMA FACIE CASE OF OBVIOUSNESS IS NOT ESTABLISHED

Claims 1-3, 5-9 and 11-15 were rejected under 35 U.S.C. §103(a) as obvious over the combined teachings of Kröger et al. *General Pharmacology*, Vol. 28, No. 2 pp. 257-263, 1997) in view of Ogata et al. (U.S. Patent No. 5,478,815) and Murdock et al. (U.S. Patent No. 4,526,788).

- A. Kroger's dosage in mice was for Intraperitoneal administration (IP), doses in humans are not for IP administration, and sufficient data is not available to compare mouse IP with human IP to extrapolate to claimed non-IP doses.**

These 3 publications neither singly nor in combination teach all elements of independent claims 1 and 13. The doses therein reflect the thrust of the invention, that "substantially lower doses" of nicotinamide and methanine prevent hepatotoxic effects.

The Kröger et al. 1997 reference entitled "Protection from Acetaminophen - induced liver damage by the synergistic action of low doses...of nicotinamide and ...N-acetylcystine or ...L-methionine" relates an attempt to mitigate acetaminophen hepatotoxicity but uses intraperitoneal administration in animals, not a method

generally used in humans, and doses that translate to higher non-IP doses in humans, than in the present claims. The end point is release of glutamate-pyruvate transaminase (GPT) and glutamate-oxaloacetate transaminase (GOT).

Kroger (1997) injected mice intraperitoneally with a composition of a acetaminophen and methatrexate with combinations of nicotinamide and methionine. Doses of 12.5 mg/kg IP were said to provide protection. Activities of GOT + GPT were determined in mice to determine if there were hepatoprotective effects.

The examiner admitted that

Kroger differs from the claimed invention in (i) the preparation of a composition comprising acetaminophen, nicotinamide and methionine in the specific amounts, namely about 80-1000 mg dose of acetaminophen, about 5 mg to about 500 mg dose of methionine and about 10 mg to about 500 mg dose of nicotinamide, per standard dose, (ii) the preparation of said composition in various dosage forms, namely oral or sterile solutions or suspensions form, more preferably tablets, capsules, caplets, intradermal, subcutaneous, intramuscular, intravenous or intrathecal.

(Office Action, December 19, 2008, p. 4.)

The examiner argued without support that those of skill in the art could extrapolate from doses for IP administration to mice in Kroger to doses and non-IP routes of administration suitable for humans.

Three elements of the pending claims for which there is no dispute that are not expressly taught by Kroger, are not predictable:

1. Route of administration – In Kroger, nicotinamide or methionine or their combination are administered intraperitoneally ("IP"). This is a very substantive difference from the routes of administration claimed in the present application. First, IP is virtually never used in humans^{2,3} for two principal reasons: (a) IP provides significantly faster and more

² Goodman & Gilman, "The Pharmaceutical Basis of Therapeutics, "Ninth Edition," 1996, pp. 8-9.

³ Remington's *Pharmaceutical Sciences*, 17th Edition, 1985, p. 784.

substantial blood levels of drugs^{1,4} than other routes of administration; and (b) risk of infection and local adhesions are unwarranted for use of this route in humans¹. There are no drugs approved for IP administration to humans in North America or Europe.

2. Composition and Method – In Kroger, nicotinamide and/or methionine are administered as separate IP injections, and the acetaminophen and methotrexate are administered orally or by IP respectively at an earlier time point. In contrast, in the compositions cited in the pending application, all components (the hepatotoxic active drug agent and the hepatoprotective agents - nicotinamide, methionine, and folic acid) are provided in the same dosage form and administered together in this dosage form (e.g. capsule, tablet, solution).
3. The dosages of nicotinamide and methionine administered IP for protective effects by Kroger are very substantially greater than those administered orally or by injection (but not IP), in the present application. IP dosages used by Kroger range from 25-100 mg/kg nicotinamide and 50-300 mg/kg methionine when each is given alone, to 12.5 mg/kg of each when they are both administered in separate IP injections. Based on the average body weight for adult Americans⁵ the dosage of nicotinamide in the claims of the present application ranges from .11 mg/kg to 5.7 mg/kg for males and from .13 mg/kg to 6.7 mg/kg for females, and the dosage of methionine in claims of the present application ranges from .29 mg/kg to 5.7mg/kg for males and from .33 mg/kg to 6.7 mg/kg for females. In contrast, IP injection results in much higher and much faster peak blood levels of drug. In the present application, these dosages are provided orally or by injection **not into** the peritoneum. Consequently, the dosages of nicotinamide and methionine in present claims are minuscule compared to those published by Kroger.

⁴ Gerasimov, M.R. et al., "Comparison Between Intraperitoneally and Oral Methylphenedate Administration, *Pharmacol. Ex. Ther.* 295: 51-57, 2000.

⁵ "National Health and Nutrition Examination Survey, "U.S. CDC National Center for Health Statistics, 2002.

The examiner argues those of skill would find it obvious to extrapolate from mouse IP doses, to human IP doses, and then extrapolate to lower doses for other routes of administration. However, because IP dosages are rare in humans, not enough data points exist to reliably extrapolate to yield "low" doses for non-IP administration.

The discussion of these differences renders it clear that Kröger (1997) does not teach that much lower dosages of nicotinamide and methionine, administered in a single dosage form with a hepatotoxic drug (e.g. in a capsule, tablet, solution), given by completely different routes of administration than Kröger, would provide safe and effective hepatoprotection from a hepatotoxic drug.

In addition, Table 5, p. 205 of H. Kröger et al. General Pharmacology 33:203-206, 1999 demonstrates that administering 50 mg/kg of nicotinamide intraperitoneally to mice along with 50 mg/kg methotrexate and 50 mg/kg acetaminophen produced significantly higher GOT and GPT elevations (increased liver toxicity) versus mice receiving 50 mg/kg methotrexate plus 50 mg/kg acetaminophen alone. Additionally, Table 5 demonstrates that higher doses of nicotinamide (i.e. 100 mg/kg and 250 mg/kg) given to the mice in conjunction with methotrexate and acetaminophen, while not increasing liver toxicity as did 50 mg/kg of nicotinamide, nonetheless provided no protection against combined methotrexate/acetaminophen-induced liver toxicity. Consequently, despite conclusions stated in the publication, Kröger teaches away from the present application regarding nicotinamide's protective effects. Kröger teaches that nicotinamide is non-hepatoprotective at high nicotinamide dosages, and at lower nicotinamide dosages, nicotinamide increases liver damage from methotrexate and acetaminophen.

B. An argument raised by appellant has not been rebutted in the record.

Kröger et al. 1999, a publication cited by the European examiner in a related case (see Supplemental IDS filed October 20, 2008) taught away from the present invention. The argument was presented on page 8, second paragraph of the Amendment mailed on April 9, 2009. However, the Examiner neither refuted nor responded to this point in the final Office Action mailed August 6, 2009.

In the Advisory Action mailed October 5, 2009, the examiner did not deny ignoring appellants' arguments based on Kroger (1999) but admitted "the examiner has not (fully) considered Kroger '99 reference..." but excuses this omission by saying that examination of the present application was limited to "acetaminophen as the hepatotoxic compound," and Kroger '99 "discussed the activity of methionine and/or nicotinamide in reducing essentially the liver toxicity of methotrexate." The examiner did not note that Kroger (1999) also gave the mice acetaminophen, although at a non-hepatotoxic dose with the methotrexate. (Abstract; col. 2, p. 203)

Since the Examiner did not consider this point, Appellant would like to again emphasize that in Table 5, page 205 of the H. Kröger et al. *General Pharmacology* 33:203-206, 1999 publication, it is demonstrated that administering 50 mg/kg of nicotinamide intraperitoneally to mice along with 50 mg/kg methotrexate and 50 mg/kg acetaminophen produced (increased) liver toxicity as shown by significantly higher GOT and GPT elevations, compared to mice receiving 50 mg/kg methotrexate plus 50 mg/kg acetaminophen alone, noting that elevated aspartate aminotransferase (GPT) and glutamate-oxaloacetate transaminase (GOT) are indicators of liver damage. Additionally, Table 5 demonstrates that higher doses of nicotinamide, nonetheless provided no protection against combined methotrexate/acetaminophen-induced liver toxicity. Consequently, Kröger teaches that **nicotinamide is non-hepatoprotective** at high nicotinamide dosages, and at lower nicotinamide dosages, **nicotinamide increases liver damage** from methotrexate and acetaminophen.

Independent claims 1 and 13 relate a composition including a hepatotoxic compound with methionine and nicotinamide. The claim elements as amended are not taught or suggested by the 1997 publication which teaches ameliorating hepatotoxicity, when the authors in a further report (Kröger et al., 1999) demonstrate that nicotinamide at certain doses is ineffective and even counterproductive to mitigating hepatotoxicity. It is appellant's position that those of skill in the art would not be guided to the present invention after consultation of the single Kröger 1997 reference in the abstract without considering the body of Kröger work, including the 1999 findings, if they were trying to develop a composition that includes a

hepatotoxic compound but mitigates its adverse effects. The data in the Kröger et al 1999 reference teaches the direct opposite of the present application regarding nicotinamide's protective effects.

C. Ogata and Murdock do not supply what is missing in Kroger (1997)

The deficiencies of the Kröger et al 1997 publication are not cured by addition of the Ogata et al. and Murdock et al. publications. The Examiner stated that these publications have been cited to demonstrate: 1) routine knowledge of using intraperitoneal (IP) injection as experimental animal testing; and 2) to demonstrate routine knowledge in calculating human dosage based upon the interrelationship of dosages for animals of various sizes and species, and humans, respectively.

According to the examiner, Ogata and Murdock are cited for "routine knowledge" of IP, and "routine knowledge" of calculating human dosages from animal studies. The unpredictability of animal testing reported in Hua et al. (1997); U.S. Dept. HHS, FDA (2009) and U.S. Dept HHS FDA (2007) indicates that results of clinical studies that are the basis for present claims, are not obvious over animal studies, and Exhibit H shows IP is not employed for treatment of humans.

1. To demonstrate that known doses of pharmaceutical compositions are not predictable from animal studies, Hua et al. (1997) contains a publication regarding the oral animal analgesic study of the proprietary drug civamide and the protocol for the Phase I human study on civamide by Winston Laboratories, Inc. (assignee of the pending application). As can be seen in the publication, in the study utilizing standard analgesic models in animals with oral dosages of 20-200 mg kg civamide, only the 200 mg/kg dose was effective. Since animal dosages bear a very uncertain relationship to human dosages, the Phase I protocol approved by FDA called for single maximum doses of 5 mg or 10 mg, which are approximately equivalent to from 0.063 to 0.126 mg/kg in humans. This is a difference of over 1,000 times less

- than the animal dosage per kg in the published oral analgesic study. Therefore, human doses were not predictable from animal results.
2. FDA, U.S. Dept. HHS (2009) Guidance for Industry on Animal Models. Note lines 108 and 109 which state “the Agency’s recognition that many treatments that appeared effective in animals have not proved to be effective in humans.”
 3. FDA, U.S. Dept. HHS (2007) Guidance on Drug-Induced Liver Injury (“DILI”). Note line 99 which states, the “The drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals.”
 4. Equivalent Surface Area Dosage Conversion Factor is the table Examiner Kwon provided as an authoritative “rule of thumb” to convert animal dosages to human dosages. As Dr. Bernstein pointed out in the USPTO interviews, this table refers to only surface area conversion factors and thus is relevant (although not accepted by experts in the field) only to topically applied medications, not systemic doses as claimed herein.
 5. Goodman and Gilman (1996) is composed of discussions of routes of administration of human drugs from Goodman & Gilman “The Pharmacological Basis of Therapeutics” (Ninth Edition) and from the 17th (1985) and 21st (2005) editions of “Remington’s Pharmaceutical Sciences.” All of these exhibits make clear that the intraperitoneal route of administration is not employed in human subjects. Additionally, there is not a single drug for intraperitoneal administration approved by the FDA. Goodman & Gilman and Remington are authoritative references in their fields (as opposed to a highly dubious citation from Wikipedia by Examiner Kwon). Therefore Kroger, who used intraperitoneal injections in mice only applied to a mouse model.

Ogata et al. and Murdock et al. neither teach nor suggest the effective combination presently claimed. Therefore, Appellant asserts that the combined teachings of the cited publications do not render the aspects of the invention as set forth in independent claims 1 and 13, obvious. The more specific dependent claims

are also not rendered obvious by the combined teachings of the cited reference for the same reasons.

Moreover, Appellant notes that the examiner had found previously found claims 13-15 to be allowable in the Office Action dated February 28, 2008, although the indication of allowability was withdrawn without explanation in the Office Action dated December 19, 2009.

A determination of obviousness requires that “the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.” *KSR International Co. v. Teleflex, Inc.*, -- U.S. --, 127 S.Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007) *quoting Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). In making a determination of obviousness by looking at the teachings of multiple patents, one should consider

the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. **To facilitate review, this analysis should be made explicit.**

KSR, 127 S.Ct. at 1740-41 (*emphasis added*). “[A] patent composed of several elements is not proved obvious merely by demonstrating the each of its elements was, independently, known in the prior art.” *Id.* at 1741.

Applicant requests that the rejection under 35 U.S.C. §103(a) over Kröger et al. 1997, Ogata et al. and Murdock et al. be withdrawn.

Reversal of the Examiner is therefore clearly in order and is solicited.

A one-month extension of time until January 7, 2010, is requested. Please charge the Deposit Account No. 12-0913 for the one-month extension fee with respect to our Atty. Docket No. 41959-102739.

No other fees are due. However, please charge any fees that might be due in connection with this submission to our Deposit Account No. 12-0913 with respect to Atty. Docket No. (41959-102739).

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Alice O. Martin", is written over a horizontal line.

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Date: January 4, 2010

Claims Appendix

1. A composition consisting essentially of one or more compounds at doses known to be hepatotoxic combined with about 5 mg to about 500 mg methionine along with about 10 mg to about 500 mg nicotinamide in a pharmaceutically acceptable carrier used in treatment of human disease.
2. The composition of claim 1 wherein said composition is suitable for oral ingestion.
3. The composition of claim 2 wherein said composition is selected from the group consisting of a solution, suspension, tablet, capsule and caplet.
4. (Cancelled)
5. The composition of claim 3 wherein said composition is selected from the group consisting of a sterile solution and a suspension.
6. The composition of claim 5 wherein said composition is suitable for intradermal, subcutaneous, intramuscular, intravenous or intrathecal injection.
7. The composition of claim 1 wherein folic acid is also present in an amount of about 50 mcg to about 5 mg per standard dose.
8. The composition of claim 7 wherein said composition is suitable for oral ingestion.
9. The composition of claim 8 wherein said composition is selected from the group consisting of a solution, suspension, tablet, capsule and caplet.
10. (Cancelled)
11. The composition of claim 9 wherein said composition is selected from the group consisting of a sterile solution and a suspension.
12. The composition of claim 11 wherein said composition is suitable for intradermal, subcutaneous, intramuscular, intravenous, or intrathecal injection.
13. A composition consisting essentially of one or more standard doses of a hepatotoxic compound, wherein said hepatotoxic compound is selected from the group consisting of acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium, and valproic acid and wherein the hepatotoxic compound is combined with about 5 mg to about 500 mg methionine along with

about 10 mg to about 500 mg nicotinamide in a pharmaceutically acceptable carrier used in treatment of human disease.

14. The composition of claim 13 wherein said hepatotoxic compound is acetaminophen.

15. The composition of claim 14 wherein said acetaminophen is present in the amount of about 80-1000 mg per standard dose.

- 16. (Withdrawn)
- 17. (Withdrawn)
- 18. (Withdrawn)
- 19. (Withdrawn)
- 20. (Withdrawn)
- 21. (Withdrawn)
- 22. (Withdrawn)
- 23. (Withdrawn)
- 24. (Cancelled)
- 25. (Withdrawn)
- 26. (Withdrawn)
- 27. (Withdrawn)
- 28. (Withdrawn)
- 29. (Withdrawn)
- 30. (Withdrawn)
- 31. (Withdrawn)
- 32. (Withdrawn)
- 33. (Withdrawn)
- 34. (Withdrawn)
- 35. (Withdrawn)
- 36. (Withdrawn)
- 37. (Withdrawn)

Evidence Appendix

1. Kroger et al. *Gen. Pharm.*, (1997), Vol. 2: 257-263).
2. Kroger et al., Vol. 33: 203-206 (1999).
3. Ogata et al. (USP 5478815).
4. Murdock (USP 4526788).
5. Goodman & Gilman, *The Pharmaceutical Basis of Therapeutics*, Ninth Edition, 1996, pp. 8-9.
6. Remington's *Pharmaceutical Sciences*, 17th Edition, 1985, p. 784.
7. Gerasimov, M.R. et al., "Comparison Between Intraperitoneally and Oral Methylphenedate Administration", *Pharmacol. Ex. Ther.* 295: 51-57, 2000.
8. National Health and Nutrition Examination Survey, U.S. CDC National Center for Health Statistics, (2002).
9. Hua et al. "Antinociception induced by civamide, an orally active capsaicin analogue" *Pain* 71:313-322, (1997)
10. FDA, U.S. Dept. HHS (2009) *Guidance for Industry*.
11. Equivalent Surface Area Dosage Conversion Factors (2007).
12. FDA, U.S. Dept. HHS (2007) *Guidance for Industry*.
13. Winston Laboratories Protocol WL 10010301 (2008).

Related Proceedings Appendix

None.